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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/527,422	03/27/2006	Birke Bartosch	P08575US00/BAS	4780

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EXAMINER	
POPA, ILEANA	
ART UNIT	PAPER NUMBER
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/527,422	BARTOSCH ET AL.	
	Examiner	Art Unit	
	ILEANA POPA	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 June 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-90* is/are pending in the application.

4a) Of the above claim(s) *57,67,71-81 and 88-90* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *46-56,58-66,68-70 and 82-87* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *14 March 2005* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Applicant's election with traverse of the invention of Group I, drawn to a method of producing infectious hepacivirus-like particles *ex vivo* and of the species of native E2 in the reply filed on 06/13/2008 is acknowledged. The traversal is on the ground(s) that the novel subject matter recited in Group I is also recited in Groups II-V. Specifically, the elected Group I and selected species, native E2 protein, as recited in claims 52, 53 and 64, include subject matter in which mutated E2 protein is either an E2 protein deleted from its C-terminal amino-acid residue and a native E2 protein, wherein the hypervariable region 1 (HRV1) has been deleted. The E2 protein deleted from its C-terminal amino-acid residue differs from full length E2 protein only by the last amino-acid residue. Therefore, the sequence of the mutated E2 protein is encompassed in the sequence of the whole native E2 protein, thus differing by the addition of a single amino-acid residue. Accordingly, searching for the whole protein native E2 protein necessarily results in searching for the one amino- acid truncated mutated E2 protein of claims 57 and 67. Further, the HRV1 domain is clearly identified (see, e.g., SEQ ID NO:16) and is composed of only 26 amino acids, whereas the sequence of the full-length E2 protein is composed of more than 360 amino acids. Therefore, a search of the E2 protein, wherein HRV1 is deleted, the sequence of which is about 93% identical to the sequence of the full-length E2 protein, should give similar results to a search performed on the full-length E2 protein. Accordingly, the field of search of these

mutated proteins is the same or substantially identical to the native protein. Therefore, no undue burden or additional search is required in order to examine all claims. Finally, the specification discloses that a 10 to 50 fold enhancement of infectiosity was observed with the HCV pseudo-particles harboring the C-terminally truncated E2 protein (see present specification, page 8, lines 33 and 34) and that hepacivirus pseudo-particles containing an E2 glycoprotein wherein HRV1 was deleted still remained infectious (see present specification, page 9, lines 8-10). Accordingly, the same prior art relating to the production of infectious hepacivirus-like particles is likely to be applicable to both species of native and mutated E2 proteins and searching them together would not be a burden for the Examiner. Finally, Applicant argues, the International Preliminary Examining Authority, in issuing its International Preliminary Examination Report, did not find a lack of unity of invention (see the attached International Preliminary Examination Report, Part 3, Box IV, "Lack of unity of invention," which is not marked). Thus, the entity with expertise in determining whether an application lacks unity of invention has found no lack of unity of invention in the present application. This is not found persuasive because the claims are drawn to multiple methods and thus the invention lacks unity (see the restriction requirement(. The argument that the International Preliminary Examining Authority did not find lack of unity is not found persuasive because this is a distinct examination; making such an argument is not proper. With respect to the species election, Applicant argues that the same prior art relating to the production of infectious hepacivirus-like particles is likely to be applicable to both species of native and mutated E2. In response to this argument, it

is noted that a search in the patent and non-patent literature for the native E2 protein did not render results relevant for the other species. Therefore, each species requires a different search and a different examination. For this reason, examining all species together would be a burden for the Examiner.

The requirement is still deemed proper and is therefore made FINAL.

Claims 57, 67, 71-81 and 88-90 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected inventions and species, there being no allowable generic or linking claim.

Claims 46-56, 58-66, 68-70, and 82-87 are under examination.

Double Patenting

2. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees.

A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

3. Claims 46-56, 58-66, 68-70, and 82-87 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-8, 10-16, 18, 27, 28, and 30 of copending Application No. 10/547,750, in view of Lechmann et al. (Hepatology, 2001, 34: 4117-423). Although the conflicting claims are not identical, they are not patentably distinct from each other because they are obvious variants.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

The instant claims are drawn to **(i)** a method of producing infectious hepacivirus-like particles (i.e., flavivirus-like particles) by providing a first nucleic acid comprising a packaging competent retroviral-derived genome, a second nucleic acid comprising a cDNA encoding core proteins from the retrovirus, a third nucleic acid comprising a cDNA encoding a polyprotein having successively a signal peptide from a type I membrane protein (such as the signal peptide derived from the heapcivirus core protein), a hepacivirus E1 protein and/or a hepacivirus E2 protein, transfecting host cells with the nucleic acids above, maintaining the transfected cells in culture to allow the expression of the structural proteins encoded by the nucleic acids, and allowing the expressed proteins to form virus-like particles; the polyprotein further comprises the core protein from hepacivirus and the hepacivirus is HCV; the packaging competent retroviral-derived genome and core proteins could be derived from MLV or HIV, the

nucleic acid encoding the polyprotein could further comprise a cDNA encoding a hepacivirus p7 protein, and the nucleic acid comprising the packaging competent retroviral-derived genome further comprises a transgene (claims 46-56, 58, and 70), **(ii)** a composition and a vaccine comprising the infectious hepacivirus particle as obtained above (claims 59-66, 68, 69, and 82), **(iii)** a method for the *in vivo* or *in vitro* transferring a transgene into a cell (claim 83), and **(iv)** a transformed host cell comprising a first nucleic acid comprising a packaging competent retroviral-derived genome, a second nucleic acid comprising a cDNA encoding core proteins from the retrovirus, a third nucleic acid comprising a cDNA encoding a polyprotein having a signal peptide from a type I membrane protein, a hepacivirus E1 protein and/or a hepacivirus E2 protein, wherein the nucleic acid encoding the polyprotein could further comprise a cDNA encoding the HCV p7 protein (claims 84-87). The specification defines that E1 and E2 are the two hepacivirus envelope proteins (p. 1, lines 24-30).

The application claims recite **(i)** a method for producing flavivirus-like particles by providing a first nucleic acid comprising a packaging competent retroviral-derived genome, a second nucleic acid comprising a cDNA encoding core proteins from the retrovirus, a third nucleic acid comprising a cDNA encoding a polyprotein having successively a flavivirus core protein (i.e., having a type I membrane protein signal peptide), a flavivirus prM proteins and/or a flavivirus E protein, transfecting host cells with the nucleic acids above, maintaining the transfected cells in culture to allow the expression of the structural proteins encoded by the nucleic acids, and allowing the expressed proteins to form virus-like particles; the core protein comprises a signal

peptide (i.e., a signal peptide derived from a type I membrane protein), the packaging competent retroviral-derived genome and core proteins could be derived from MLV or HIV, and the nucleic acid comprising the packaging competent retroviral-derived genome further comprises a transgene (claims 1-8 and 10), **(ii)** an infectious flavivirus-like particles and a vaccine comprising the particles, wherein the particles are obtained by the above method (claims 11-16, 18, and 27), **(iii)** a method for the *in vitro* transferring a transgene into a cell (claim 28), and **(iv)** a transformed host cell comprising a first nucleic acid comprising a packaging competent retroviral-derived genome, a second nucleic acid comprising a cDNA encoding core proteins from the retrovirus, a third nucleic acid comprising a cDNA encoding a polyprotein having a flavivirus core protein, a flavivirus prM proteins and/or a flavivirus E protein (claim 30). The specification defines that the flavivirus could be a hepacivirus such as HCV and that prM and E are the flavivirus envelope glycoproteins (i.e., E1 and E2 when the flavivirus is HCV) (p. 1, lines 9-20, p. 4, lines 29-33, p. 5, lines 1, 2, 31, and 32, p. 6, lines 1-4). The application claims do not recite p7. Lechmann et al. teach obtaining HCV-like particles which particles could further comprise p7 induce and which particles could induce both humoral and cellular immune responses (Abstract, p. 417, column 2). It would have been obvious to one of skill in the art, to modify the application claims by further including p7 in an HCV-like particle to obtain the predictable result of obtaining a vaccine capable of inducing immune responses. Since the application claims embrace all the limitations of the instant claims, the application claims and the instant claims are obvious variants.

Claim Rejections - 35 USC § 112, 2nd paragraph

4. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claim 54 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 54 recites the limitation "p7 protein" in 47. There is insufficient antecedent basis for this limitation in the claim. Amending the claim to make it dependent from claim 53 would obviate the rejection.

6. Claim 70 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Specifically, claim 70 recites a "signal peptide from a type I membrane protein, preferably a hepacivirus core protein". A preferred embodiment may be set forth in another dependent claim; when stated in a single claim, preferences lead to confusion over the intended scope of the claim. Since it is not clear whether the claimed preferred embodiment (i.e., the signal peptide from the hepacivirus core protein) is a claim limitation, the metes and bounds of the claims cannot be determined and the claim is indefinite.

Claim Rejections - 35 USC § 103

7. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

8. Claims 46-56, 58-66, 68-70, and 82-87 are rejected under 35 U.S.C. 103(a) as being unpatentable over Marasco et al. (WO 00/55335), in view of both Lechmann et al. (Hepatology, 2001, 34: 4117-423) and Ray et al. (FEMS Microbiology Letters, 2001, 202: 149-156).

Marasco et al. teach an *ex vivo* method of producing infectious virus-like particles such as a flavivirus-like particle by **(i)** providing a packaging retroviral vector comprising a transgene and the cis-acting elements necessary for encapsidation, reverse transcription, and integration (i.e., a first nucleic acid sequence comprising a packaging competent retroviral genome), a vector encoding the retroviral gag-pol (i.e., a second vector comprising a cDNA encoding retroviral the core proteins), and a vector encoding the flavivirus envelope proteins (i.e., a third nucleic acid sequence comprising a cDNA encoding the envelope proteins), and **(ii)** transfecting host cells with the vectors above, culturing the transfected host cells to express the viral proteins and form the viral particles (claims 46, 48, 58, 70, and 84) (p. 4, third full paragraph, p. 6, first and second full paragraphs, p. 7, first paragraph, p. 16, p. 12, first and third paragraphs, p. 34, last paragraph, p. 41, third and fourth full paragraphs, claims 1-3 and 6-12). Marasco et al. also teach purifying their viral particles and using them to induce immune responses or to deliver transgenes to cells (claims 59, 82, and 83) (p. 34, last paragraph, p. 35).

Although Marasco et al. teach their method as suitable to make infectious flavivirus-like particles, they do not specifically teach HCV, nor do they teach a HCV polyprotein comprising in order the core protein, the native E1 and E2 proteins, and the native p7 protein (claims 46-56, 58-66, 68-70, and 82-87). Lechmann et al. teach obtaining infectious HCV-like particles wherein the HCV-like particles are made by using a vector encoding a polyprotein comprising successively the HCV core, E1, E2 and p7 proteins (Abstract, p. 417, column 2). It would have been obvious to one of skill in the art, at the time the invention was made, to modify the method of Marasco et al. by using the polyprotein of Lechmann et al. to achieve the predictable result of obtaining infectious HCV-like particles. By including HCV core protein, one of skill in the art would have necessarily included a signal sequence because the HCV core protein comprises a signal sequence, wherein the signal sequence is required for the proper polyprotein targeting to the host cell endoplasmic reticulum (see Ray et al., p. 150, column 1 and Fig. 1). With respect to the limitation of a signal peptide derived from a type I membrane protein (claims 46 and 70), it is noted that the instant claim 70 defines that the signal sequence from a type I membrane protein could be the signal sequence from the core protein. Therefore, the combined teachings of Marasco et al. and Lechmann et al. disclose an infectious HCV-like particle obtained by using a nucleic acid sequence comprising a cDNA encoding a polyprotein containing successively a signal peptide from a type I protein, and the HCV E1, E2, and p7 proteins. Thus, the claimed invention was *prima facie* obvious at the time the invention was made.

9. No claim is allowed. No claim is free of prior art.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to ILEANA POPA whose telephone number is (571)272-5546. The examiner can normally be reached on 9:00 am-5:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach can be reached on 571-272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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